

Applicants : Alexander Gad and Dora Lis
Serial No. : 10/792,311
Filed : March 2, 2004
Page 14 of Amendment Under C.F.R. §1.116 in Response to
June 16, 2005 Final Office Action

REMARKS

Claims 123, 127-134, 138-145, 149-155 and 159-164 were pending in the subject application. By this Amendment, applicants have amended claims 123 and 144. Accordingly, claims 123, 127-134, 138-145, 149-155 and 159-164 are pending in the subject application.

Support for the amendment to claim 123 may be found *inter alia* on page 3, lines 28-31 of the subject application.

Support for the amendment to claim 144 may be found *inter alia* in column 2, lines 40-43 of U.S. Patent No. 5,800,808, the relevant text of which has been incorporated into the subject application by this amendment and on page 32, lines 15-16 of the subject application.

Initially, applicants thank Examiner P. Huynh for scheduling a telephone conference with the undersigned at 1 p.m. on Tuesday, July 26, 2005. Applicants hope the following remarks overcome the rejections of record, but to the extent the Examiner has further questions, such can be addressed during the July 26 telephone conference.

Rejection under 35 U.S.C. §102(a)

On page 2, section 5 of the June 16, 2005 Final Office Action, the Examiner maintained the rejection of claims 123, 127-128, 133-134, 138-139, 144-145, 149-150, 155 and 159-160 under 35 U.S.C. §102(b) as allegedly anticipated by U.S. Patent No. 5,800,808 ("the '808 patent") as evident by the Pharmacia Biotech Directory, citing pages 340-341.

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The Examiner alleged that the '808 patent teaches a process for obtaining a pharmaceutical product containing an aqueous mixture of polypeptides each of which consists of essentially of alanine, glutamic acid, tyrosine and lysine wherein the reference mixture has a desired average molecular weight of about 4,000-8,600 Dalton which is within the claimed average molecular weight from 4000 to 13,000 Daltons, citing col. 2, lines 8-14, in particular. The Examiner also alleged that during the process, a batch of the reference aqueous mixture of polypeptides is chromatograph on a column to such as Fractogel TSK and Superose 12 column, citing col. 3, line 6-8, to establish a relationship between retention time on the column and the molecular weight (see paragraph bridging cols 2-3, in particular). The Examiner further alleged that the reference's Superpose 12 column inherently comprises a cross-linked agarose-based medium, with an exclusion limit of 2×10^6 Daltons, an optimal separation range of 1000 to 3×10^5 Daltons and a bead diameter of 20-40 μm based on average molecular weight of the reference 4,000-8,600 Daltons which is within the claimed average molecular weight from 4000 to 13,000 Daltons and as evident by evidentiary reference Pharmacia Biotech Directory, citing page 341, in particular. The Examiner also alleged that the reference's process of obtaining the reference pharmaceutical product is by column chromatography of L-GLAT to obtain the desired average of molecular weight species, citing the Summary of Invention section, in particular.

In response, applicants maintain that the '808 patent does not anticipate the applicants' invention. Column 3, lines 6-8 of the '808 patent states, "[T]he molecular distribution

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of the 2 batches was determined on a calibrated gel filtration column (Superose 12)." No reference to "markers", much less to the specific polypeptide markers of applicants' invention, is made in the '808 patent.

Applicants reiterate that the calibration step of the claimed invention uses a plurality of molecular weight markers, each of which is a polypeptide consisting essentially of alanine, glutamic acid, tyrosine and lysine and having a predetermined amino acid sequence.

Applicants point out that a gel filtration column may be calibrated in any number of ways. For example, applicants attach hereto as **Exhibit 1** a list of calibration kits sold by the maker of the Superose 12 column (now GE Healthcare). None of the markers in the polypeptide kits are made from only four distinct amino acids, let alone the four specified in applicants' invention.¹

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. §2131 (citing Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631 (Fed. Cir. 1987)) The '808 patent does not disclose the characteristics of the molecular weight markers used, let alone teach the use of molecular weight markers consisting essentially of the four specified amino acids. As such, the '808 patent does not anticipate the applicants' invention.

¹ For example, ribonuclease A, the sequence of which is attached in **Exhibit 2**, contains many more than four amino acids.

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Accordingly, applicants request that the Examiner reconsider and withdraw the rejection of claims 123, 127-128, 133-134, 138-139, 144-145, 149-150, 155 and 159-160 under 35 U.S.C. §102(b) as allegedly anticipated by the '808 patent.

Rejection under 35 U.S.C. §102(e)

On page 3, section 6 of the June 16, 2005 Final Office Action, the Examiner maintained the rejection of claims 123, 133-134 and 144 under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 5,858,964 ("the '964 patent").

The Examiner alleged that the '964 patent teaches a process for obtaining a pharmaceutical product containing an aqueous mixture of polypeptides each of which consists of essentially of alanine, glutamic acid, tyrosine and lysine wherein the reference mixture has a desired average molecular weight of about 4,000-12,000 which is within the claimed average molecular weight from 4000 to 13,000 Daltons, citing the Summary of Invention section, col.3, lines 1-4, in particular. The Examiner alleged that the reference's process of obtaining the reference pharmaceutical product is by column chromatography of L-GLAT to obtain the desired average of molecular weight species, citing column 4, lines 8-10. The Examiner also alleged that the step of calibrating the molecular weight obtained using the column chromatography is inherent in the reference process given that the reference method produces the same desired molecular weight. The Examiner further alleged that the reference polypeptide is copolymer-1, which is also known as glatiramer acetate, citing column 2, lines 18-21. The Examiner also alleged that the reference's process

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further comprises a step of lyophilized the reference glatiramer acetate, citing column 4, line 35-36. Thus, the Examiner concluded that the reference teachings anticipate the claimed invention.

In response, applicants maintain that the '964 patent does not anticipate the applicants' invention. No reference to calibration, much less to "markers" or the specific polypeptide markers of applicants' invention, is made in the '964 patent.

Applicants reiterate that the calibration step of the claimed invention uses a plurality of molecular weight markers, each of which is a polypeptide consisting essentially of alanine, glutamic acid, tyrosine and lysine and having a predetermined amino acid sequence.

Applicants point out that a gel filtration column may be calibrated in any number of ways. For example, applicants attach hereto as **Exhibit 1** a list of calibration kits sold by the maker of the Superose 12 column (now GE Healthcare). None of the markers in the polypeptide kits are made from only four distinct amino acids, let alone the four specified in applicants' invention.²

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. §2131 (citing Verdegaal Bros. v. Union Oil Co. of

² For example, ribonuclease A, the sequence of which is attached in **Exhibit 2**, contains many more than four amino acids.

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California, 814 F.2d 628, 631 (Fed. Cir. 1987)) The '964 patent does not disclose the characteristics of the molecular weight markers used, let alone teach the use of molecular weight markers consisting essentially of the four specified amino acids. As such, the '964 patent does not anticipate the applicants' invention.

Accordingly, applicants request that the Examiner reconsider and withdraw the rejection of claims 123, 133-134 and 144 under 35 U.S.C. §102(e) as allegedly anticipated by the '964 patent.

Rejection under 35 U.S.C. §103(a)

On page 4, section 9 of the June 16, 2005 Final Office Action, the Examiner maintained the rejection of claims 123, 127-128, 134, 138-139, 145, 149-150, 155, and 159-160 under 35 U.S.C. 103(a) as allegedly unpatentable over the '964 patent in view of Pharmacia Biotech Directory, citing pages 340-341. The Examiner stated the teachings of the '964 patent have been discussed supra.

The Examiner alleged that the invention in claims 127, 138, 149 and 159 differs from the teachings of the references only in that the process for obtaining a pharmaceutical product wherein the gel permeation chromatography column comprises a cross-linked agarose-based medium, with an exclusion limit of 2×10^6 Daltons, an optimal separation range of 1000 to 3×10^5 Daltons and a bead diameter of 20-40 μm .

The Examiner alleged that the invention in claims 128, 139, 150, and 160 differs from the teachings of the references

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only in that the process for obtaining a pharmaceutical product wherein the gel permeation chromatography column is Superose 12.

The Examiner also alleged that Pharmacia Biotech Directory teaches a process of separating peptide based on sized using a Superose column such as Superpose 12 that is a media that provides high resolution gel filtration at rapid flow rates in a wide range of buffer conditions, citing page 340, column 1. The Examiner further alleged that the reference gel permeation chromatography column is a cross-linked agarose-based medium with an exclusion limit of 2×10^6 Daltons, and has an optimal separation range of 1000 to 3×10^5 Daltons and a bead diameter of 20-40 μm citing page 341, far right column. The Examiner alleged that the reference further teaches that the highly cross-linked agarose structure of Superose is suitable for separation, purification and molecular weight determination of proteins, peptides and nucleic acid, citing page 340, column 1, first paragraph.

The Examiner alleged it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the chromatography column as taught by the '964 patent for the Superose column as taught by Pharmacia Biotech Directory for a method of obtaining a pharmaceutical product based on size exclusion as taught by the '964 patent and Pharmacia Biotech Directory. The Examiner also alleged that from the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

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The Examiner also alleged that one having ordinary skill in the art would have been motivated to do this because the Pharmacia Biotech Directory teaches that the highly cross-linked agarose structure of Superose is suitable for separation, purification and molecular weight determination of proteins, peptides and nucleic acids, citing page 340, column 1, first paragraph. The Examiner further alleged that the '964 patent teaches the desired average of molecular weight of copolymer-1 or glatiramer acetate that consists of essentially of alanine, glutamic acid, tyrosine and lysine as a pharmaceutical product is about 4,000-12,000 which is within the claimed average molecular weight from 4000 to 13,000 Daltons, citing the Summary of Invention section, column 3, lines 1-4.

In response, applicants point out that neither the '964 patent nor Pharmacia Biotech Directory alone or in combination teaches or suggests use of a plurality of molecular weight markers, each of which is a polypeptide consisting essentially of alanine, glutamic acid, tyrosine and lysine and having a predetermined amino acid sequence, to calibrate a gel filtration column. As such, one skilled in the art would have no motivation to use, nor any expectation of success of using, a plurality of molecular weight markers of the subject invention for the calibration of a chromatography column based on the disclosures of the '964 patent and Pharmacia Biotech Directory.

As noted previously, the calibration step of the claimed invention uses a plurality of molecular weight markers, each of which is a polypeptide consisting essentially of alanine,

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glutamic acid, tyrosine and lysine and having a predetermined amino acid sequence. No motivation exists in the prior art for using such molecular weight markers. Furthermore, absent hindsight, the prior art offered no expectation of success of doing so. Yet furthermore, the art in any combination fails to teach every element of applicants' claims, e.g., the markers as recited in applicants' claims are not taught in any of the cited art. Indeed, the Examiner has not offered any evidence to the contrary. Therefore, applicants' invention is not obvious over the '964 patent in view of Pharmacia Biotech Directory.

Accordingly, applicants request that the Examiner reconsider and withdraw the rejection of claims 123, 127-128, 134, 138-139, 145, 149-150, 155, and 159-160 under 35 U.S.C. §103(a) as being unpatentable over the '964 patent in view of Pharmacia Biotech Directory.

Allowable Subject Matter

On page 6, section 10 of the June 16, 2005 Final Office Action, the Examiner maintained the objection to claims 129-132, 140-143, 151-154 and 161-164 as being dependent upon a rejected base claim. However, the Examiner stated that these claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

As discussed above, the rejections of base claims should be withdrawn. Applicants therefore request that the Examiner reconsider and withdraw the objections of claims 129-132, 140-143, 151-154 and 161-164.

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If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Calibration Kits

Order Information

Product	Pack size	Info	Product Code	Price
Gel Filtration LMW Calibration Kit	1		17-0442-01	country select
Gel Filtration HMW Calibration Kit	1		17-0441-01	country select
Blue Dextran 2000	10 g		17-0360-01	country select

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Superose 6 10/300 GL	1		17-5172-01	country select
HiPrep 16/60 Sephacryl S-200 HR	1		17-1166-01	country select
Disposable PD-10 Desalting Columns	30		17-0851-01	country select

Calibration Kits

Technical Information

- Protein components of the kits show ideal behavior in gel filtration and enable simple, reliable calibration of gel filtration columns.
- Available in low and high molecular weight ranges supplied lyophilized in individual vials.
- Kits include Blue Dextran 2000 to determine the column void volume and to check column packing.

SELECTION GUIDE – Calibration Kits

Gel	Kit(s)
Superose™ 12, Superose™ 6	LMW and HMW
Superdex™ 30 prep grade	LMW
Superdex™ 75, Superdex™ 75 prep grade	LMW
Superdex™ 200, Superdex™ 200 prep grade	LMW and HMW
Sephadex™ G-75, Sephadex™ G-75 SF, Sephadex™ G-100, Sephadex™ G-100 SF	LMW
Sephacryl™ S-200 HR, Sephacryl™ S-300 HR, Sephacryl™ S-400 HR	LMW and HMW

TECHNICAL SPECIFICATIONS

Quantity Apparent Mol. Weight**▪ Gel Filtration LMW Calibration Kit**

Ribonuclease A	50 mg	13 700
Chymotrypsinogen A	50 mg	25 000
Ovalbumin	50 mg	43 000
Bovine Serum Albumin	50 mg	67 000
Blue Dextran 2000	50 mg	≈ 2 000 000

Gel Filtration HMW Calibration Kit

Aldolase	50 mg	158 000
Catalase	50 mg	232 000
Ferritin	50 mg	440 000
Thyroglobulin	50 mg	669 000
Blue Dextran 2000	50 mg	≈ 2 000 000

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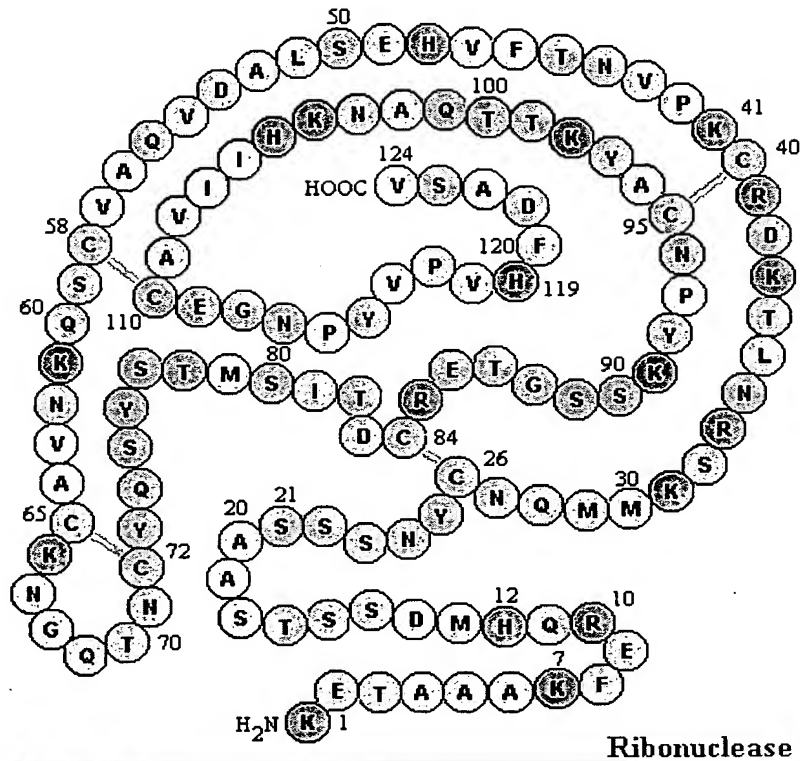
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Ribonuclease A: Amino Acid Sequence



Ribonuclease

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Amino Acids

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